Amplifying diverse voices

https://doi.org/10.1038/s41564-023-01399-7

Natural killer cells and antibodies versus malaria

Malaria is a deadly vector-borne disease caused by *Plasmodium* parasites. In 2021, the World Health Organization (WHO) reported an estimated 247 million malaria cases and 618,000 deaths, most of which occurred in children under five years of age. History was made in October 2021 when the WHO officially recommended the paediatric malaria vaccine RTS,S/AS01 for widespread use in sub-Saharan Africa, which accounts for 95% of cases and 96% of the deaths that occur due to this disease. Despite being a groundbreaking intervention against malaria, RTS,S has serious limitations that hinder its protective efficacy. The need to deepen our understanding of protective immunity to malaria thus remains critical as we strive to develop more tools that will save the lives of more African children.

The immune response to malaria is complex[1]; the parasite expresses different antigens throughout its lifecycle within the bloodstream, producing a polyclonal antibody response that becomes more protective against symptoms with repeated exposure. Natural killer (NK) cells are cytotoxic immune cells that are present in peripheral blood and are crucial to antiviral and antitumour immune responses. The ability of NK cells to mediate antimalarial immunity is increasingly recognized[2]. Several recent studies demonstrate that NK cells can kill malaria-infected red blood cells that are bound by antibodies (opsonized), through a process named antibody-dependent cellular cytotoxicity. Although antibodies against merozoites, the only stage of the parasite's lifecycle that takes place outside of the host cell, are protective against symptomatic illness, effector responses against this specific stage were never evaluated until the release of this highlighted publication.

In a recent report in *Science Translational Medicine*, Dennis Odera and colleagues from Faith Osier's group and collaborators demonstrate for the first time that NK cells can kill opsonized merozoites. Specifically, the authors exposed NK cells from malaria-naive donors to merozoites opsonized with serum from malaria-exposed individuals and measured NK cell activation by quantifying levels of degranulation (CD107a) and IFNγ. No NK cell activation occurred when merozoites were treated with serum from malaria-naive donors, indicating that merozoite-specific antibodies in the exposed serum mediate this effect. Subsequent in vitro experiments showed that merozoite-specific antibody-dependent NK cell (Ab-NK) activity occurred in a strain-independent manner and inhibited merozoite invasion into uninfected red blood cells.

Importantly, these findings were translatable to two distinct human studies. The authors first performed a retrospective analysis of pre-infection samples from a controlled human malaria infection trial in semi-immune Kenyan adults, in which participants that developed symptoms of infection or excessive parasitaemia were immediately treated. Treated participants displayed significantly lower Ab-NK activity than those who did not need treatment, showing a strong positive correlation of protection from symptomatic infection with high Ab-NK. The authors then assessed Ab-NK activity in samples from a longitudinal observational paediatric study cohort in Kenya. They noted that children generally had lower Ab-NK levels compared with adults from that area, which is unsurprising given that malaria exposure, and consequently malaria-specific antibody coverage, increases with age in endemic areas. A more rigorous statistical analysis accounting for age and previous malaria infections confirmed that high Ab-NK activity was found to be significantly associated with protection from symptomatic malaria. These findings were further corroborated with a Cox regression analysis, where the outcome was the time to the first observed malaria infection in this cohort.

A key innovative feature of this study was the approach used to evaluate the relevance of candidate malaria vaccine antigens to naturally acquired immunity. Odera and colleagues developed a plate-based assay in which recombinant proteins were incubated in serum from malaria-exposed individuals before the addition of purified NK cells. This assay could quantify Ab-NK activity in response to a series of candidate vaccine targets. Surprisingly, several well-characterized antigens (for example, PfRH5, EBA-175) did not potently activate NK cells, whereas others, including less-studied antigens, were strong Ab-NK inducers. Although this study has its limitations, it provides a method for the identification of NK-cell-activating antigens and a great foundation for deeper exploration into the role of NK cell diversity, heterogeneity and adaptation in antibody effector responses.

This study was highlighted for several reasons. First, the discovery that NK cell effector responses against whole parasites take place and are relevant to clinical immunity to malaria is significant. Second, introducing this customizable and straightforward experimental platform to evaluate the immunogenicity of recombinant proteins will facilitate malaria vaccine development and has potential to be applied more broadly to different fields. Finally, the achievement and innovation demonstrated in this study, which was led by Kenyan scientists and supported by a Kenyan principal investigator, further speaks to the invaluable contributions of African scientists in global health research. This academic community must continue to empower those who keenly understand the toll that malaria takes if we want to champion true equity in our fight to eradicate this disease.

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Competing interests

The authors declare no competing interests.

Original article: Odera, D. O. et al. Anti-merozoite antibodies induce natural killer cell effector function and are associated with immunity against malaria. *Sci. Transl Med.* **15**, eabn5993 (2023).

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